JC08 Rec'd PCT/PTO 30 MAR 2001

FORM PTO-1390 (REV. 10-96) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY DOCKET NUMBER: A-70409/RFT

U.S. APPLICATION NO. (If known, sect 37 C.F.R. 1.5): 09/806525

**"EXPRESS MAIL" MAILING CERTIFICATION**
**Number: EL821722031US Date of Deposit: March 30, 2001**
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, BOX PCT, Washington, D.C. 20231, on March 30, 2001.
Typed or Printed Name: Mark Rancifer
Signed: M Rancifer

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/GB99/03235 | 30 September 1999 | 30 September 1998 |

TITLE OF INVENTION: EGFR 37 KDA FRAGMENT AS CANCER MARKER

APPLICANT(S) FOR DO/EO/US: (1) Stephanie McKEOWN, Great Britain; and (2) Joan RITCHIE, Great Britain

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau. Form PCT/IB/308 enclosed.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information.

    Form PCT/IB/308
    International Search Report
    International Preliminary Examination Report, including Amended Sheets 15 and 16 (claims)

JC08 Rec'd PCT/PTO 30 MAR 2001

| U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.53) | INTERNATIONAL APPLICATION NO. | ATTORNEY'S DOCKET NUMBER |
|---|---|---|
| 09/806525 | PCT/AU99/00563 | A-70409/RFT |

| 17. ☒ The following fees are submitted: | CALCULATIONS | PTO USE ONLY |
|---|---|---|
| **Basic National Fee (37 CFR 1.492(a)(1)-(5)):** | | |
| Search Report has been prepared by the EPO or JPO ..... $860.00 | | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... $690.00 | | |
| No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... $710.00 | | |
| Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... $1000.00 | | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... $100.00 | | |
| **ENTER APPROPRIATE BASIC FEE AMOUNT =** | $ 860.00 | |
| Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)). | $ | |

| CLAIMS | NUMBER FILED | | NUMBER EXTRA | RATE | | |
|---|---|---|---|---|---|---|
| Total Claims | 20 | -20 = | 0 | X $ 18.00 | $ 0.00 | |
| Independent Claims | 7 | -3 = | 4 | X $ 80.00 | $ 320.00 | |
| Multiple dependent claims (if applicable) | | | | + $ 270.00 | $ 270.00 | |
| | | | | **TOTAL OF ABOVE CALCULATIONS =** | $ 1,450.00 | |
| Applicant hereby claims small entity status. See 37 CFR 1.27. Reduction by 1/2 for filing by small entity. | | | | - | $ 725.00 | |
| | | | | **SUBTOTAL =** | $ 725.00 | |
| Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). | | | | + | $ | |
| | | | | **TOTAL NATIONAL FEE =** | $ 725.00 | |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property | | | | | $ | |
| | | | | **TOTAL FEES ENCLOSED =** | 725.00 | |
| | | | | Amount of refund: | $ | |
| | | | | charged | $ | |

a. ☒ A check in the amount of $725.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 06-1300 in the amount of $ _____ to cover the above fees.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Order No. A-70409/RFT)

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

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# EGFR 37 KDA FRAGMENT AS CANCER MARKER

The present invention relates to a method of diagnosis of bladder cancer or prostate cancer and to a method of detecting recurrence of bladder or prostate cancer. More particularly the invention relates to an accessible marker.

Transitional cell carcinoma (TCC) of the bladder accounts for 1% of all cancers and is the fifth most common malignancy in people over the age of sixty in industrialised parts of the world (Russell et al., 1988; Gleave et al., 1993). Eighty percent of all bladder TCC is superficial at presentation; the remaining 20% is muscle invasive and 50% of patients in this category die despite treatment (Simoneau and Jones, 1994). Of those patients initially presenting with superficial tumours, 50 to 70% have recurrences within two years. These recurrences are usually superficial, although 10 to 20% progress to the muscle invasive form (Parmer et al., 1989; Fradet, 1992; Harland, 1994).

The high frequency of recurrent TCCB and the increase in disease status in a proportion of patients means

that lifetime follow-up using cystoscopy and urinary cytology is essential. The standard procedure is an initial check cystoscopy three months after disease presentation; if this is clear cystoscopy should then be carried out every six months, for one to two years and then annually thereafter with a flexible cystoscope. At present the recurrence rate of TCCB means that annual lifetime cystoscopies should be carried out for all stabilised patients.

Cystoscopy involves insertion of a cystoscope into the bladder via the urethra to allow visualisation of the tumour using fibre optics. It confirms clinically and pathologically the presence of tumour within the bladder and allows a morphological description (Hossan and Striegal 1993). However it has the disadvantages of being an invasive, uncomfortable procedure. The frequent recurrences of TCCB mean that patients must undergo lifetime follow-up using cystoscopy; this results in the further disadvantage of a large expenditure by the health service.

Urine cytology is used for the detection of recurrent bladder TCC and although it offers the advantages of being a non-invasive, inexpensive, easily accessible procedure (Zein and Milad, 1991), it has a poor sensitivity, especially at lower stages and grades of disease. The result is false positive and negative findings with reported sensitivities ranging from 37.9% (Miyanaga eta al., 1997) to 64% (Martins et al., 1997).

Numerous studies have been carried out to find the ideal bladder cancer marker. However, none are adequately sensitive or specific enough to fulfil a diagnostic role at present. The most successful to date appears to be the Bard BTA, STAT and TRAK tests

with overall sensitivities of 55% (Bard promotional information), 72% (Leyh et al., 1997) and 88% (Bard promotional information) respectively.

Bladder cancer is a frequently recurring disease; patients require lifetime monitoring using cystoscopy and urinary cytology. Cystoscopy is an invasive technique and urinary cytology while non-invasive has a low sensitivity.

It is an aim of the present invention to replace these two procedures with a sensitive, non-invasive urinary test which would allow detection of first presentation and recurrent bladder cancer.

The invention relates to the presence of a 37KDa epidermal growth factor receptor (EGFR) fragment in the urine of patients with transitional cell carcinoma of the bladder (TCCB) and in the urine of some patients with prostate cancer.

This fragment had not previously been detected and its presence permits the development of a novel and inventive diagnostic test.

The 37KDa fragment can be observed in a western blot of proteins from a urine sample from a patient with TCCB.

According to the present invention there is provided a marker for bladder cancer, the marker comprising a 37KDa EGFR fragment which is detectable in urine.

The marker may also or alternatively be used as a marker for prostate cancer.

The invention provides a test for the presence of a

37KDa EGFR fragment in urine, the test comprising detecting the 37KDa EGFR fragment with an antibody. The test may comprise a western blot assay.

Alternatively the test may comprise an immunochromatographic assay, an ELISA test, latex agglutination or radioimmunoassay.

The invention further provides a method of diagnosing bladder cancer or prostate cancer or detecting recurrence of these, the method comprising the steps of reacting a urine sample from an individual to be tested with means to detect a 37KDa EGFR fragment and analysing results.

Herein the term "diagnosing" relates to first presentation diagnosis and detection of recurrence.

In one embodiment the means to detect the 37KDa EGFR fragment is an antibody.

Preferably the antibody is raised against a peptide corresponding to amino acid residues 1005 to 1016 of EGFR or binds to such a peptide or a peptide substantially similar thereto.

A substantially similar peptide is 60% homologous to the amino acid sequence along at least 50% of the length of the 37KDa peptide.

In a particular embodiment of the invention the antibody is Ab4 EGFR antibody available from Oncogene Science, Inc.

The invention further provides the use of antibody Ab4 EGFR in a test to detect the present of 34KDa EGFR

fragment in urine.

The invention also encompasses the use of specific antibodies raised to the 37KDa fragment of EGFR.

In one embodiment the test is in the form of a dip stick.

The test can be used in conjunction with other appropriate tests to diagnose TCCB, prostate cancer and urinary infection.

**Experiment 1**

A 37KDa EGFR fragment has been detected in urine from patients with bladder cancer. First morning urine samples were collected from 24 TCC patients, 6 patients who had bladder cancer previously but who were now disease free and 13 healthy volunteers. 10mls of urine from each was freeze dried and the powdered residue reconstituted in Laemmli lysis buffer. After heating at 110°C for 20 minutes, all samples were stored at -70°C until required for analysis. Samples were then probed with the Ab4 EGFR antibody (Oncogene Sciences) to the internal domain of the receptor by western blot analysis.

| Disease Status | No | Presence of the 37KDA Fragment | Absence of the 37KDA Fragment |
|---|---|---|---|
| Healthy | 13 | 1 | 12 |
| TCC | 24 | 21 | 3 |
| Remission (disease free) | 6 | 4 | 2 |

A 37KDa fragment was detected in 88% (21/24) of TCC patients, 66% (4/6) of disease free patients and 7% (1/13) of healthy volunteer urine samples. There was

an overall significant association between detection of the 37KDa fragment and presence of bladder cancer. Although four out of six patients who were though to be disease free tested positively, two had frank low grade tumours and two had bladder inflammation at the time the urine sample was taken. This 37KDa fragment therefore appears to be of diagnostic importance. It has a much higher sensitivity than urinary cytology and the Bard BTA and STAT tests, and it appears to be comparable to the Bard TRAK test.

**Experiment 2**

| Disease Status | Number† | Presence of the 37KDA Fragment | Absence of the 37KDA Fragment | $(CHI)^2$ |
|---|---|---|---|---|
| Healthy | 25(13) | 1(4%) | 24(96%) | |
| Urinary Infection | 16(12) | 10(62.5%) | 6(37.5%) | |
| Remission (disease free) | 6(2)‡ | 0 | 6(100%) | 46.17* |
| TCC | 32(24) | 28(87.5%) | 4(12.5%) | |
| Prostate Cancer | 10(0) | 5(50%) | 5(50%) | |

**Sensitivity levels for the detection of a 37KDa EGFR fragment in urine.**

* denotes significant ($p<0.001$); †number in brackets is the number originally reported.

‡ This is somewhat different from Experiment 1 - the 6 so called remission patents were in fact all in remission when the notes were checked.

In fact: two were in remission, BUT two had

inflammation and two frank low grade tumour - and have been reassigned. Four more patients who are definitely in remission at the time of the test were added and there are now 6 confirmed remission patients with no marker.

Overall the second study has increased the number by a small amount and the data is holding up well. A group of prostate cancer patients has been added in since males often have undiagnosed prostate cancer. This could be a confounding factor as 50% are positive. However there is a blood test for prostate cancer so this would have to be carried out on positive patients along with a check for infection.

It is possible that the 37KDa protein could be used to distinguish between stage or grade in prostate cancer. The biology of prostate should be clarified and then collated with the patients tested. The test could be used as a general screen for health in the genitourinary area since it might pick up silent bladder and prostate tumours and infection - a positive test could lead to other tests to rule these possibilities out.

**Comment on the table:**

- shows 87.5% of TCC patients tested positive for the protein, whereas in contrast only 4% of the healthy controls expressed this protein in urine

- those patients in disease free (in remission), 100% tested negative

- the urinary infection group, 62.5% of the patients tested positive and 37.5% tested negative

- 50% of the prostate cancer patients test positive

- to date, the overall sensitivity of the 37KDa protein is 87% and the specificity is 96%.

- statistical analysis shows that detection of the 37KDa fragment is dependent on the presence of disease ($chi^2$=46.17 $p<0.001$).

**Detection of the 37KDR EGFR fragment in urine**

From the investigations carried out on the detection of the 37KDa EGFR fragment, it has been statistically established that the detection of the protein is dependent on disease presence. The fact that all remission patients analysed, tested negative for the 37KDa fragment is very encouraging. To date the overall sensitivity of the fragment protein is 87% and the specificity is 96%. Both these figures are superior to those of the BTA stat and the NMP22 tests which are commercially available. The sensitivities for the NMP22 and the BTA stat are 48% and 57% respectively, with specificites of 70% and 68% respectively (Weiner *et al*, 1998). However, the 37KDa EGFR fragment test is not 100% sensitive or specific. The test did not pick up 4 patients who had bladder tumours at the time of analysis. It may therefore be suggested that the 37KDa test could be used in tandem with both the NMP22 and the BTA stat test to reach 100% sensitivity and specificity. If 2 out of 3 of the tests gave positive results for a particular patient, it could be predicted that the patient had a bladder tumour. However, this hypothesis needs to be researched further, in order for this statement to be confirmed.

The test of the present invention may be used alone or together with any other suitable test.

Of the prostate patients analysed, 50% tested positive for the 37KDa fragment. The medical records of these patients will have to be researched further to confirm if they also had a undetected bladder tumour at the time of urine analysis. If it is found that these patients did not have bladder cancer, they could be ruled out by performing the prostate-specific antigen (PSA) test.

From the data obtained it was also found that 57% of urinary infection patients tested positive for the 37KDa fragment. This was to be expected, as EGFR over expression has been associated with inflammation and chronic irritation (Uhlman *et al.*, 1996). The urinary infection patients would have to be treated with a course of antibiotics before the 37KDa test could be carried out. The 37KDa fragment test has a number of clinical uses. Firstly, the test could be used to determine whether or not a patient requires cystoscopy. This would cut down on the number of cystoscopies presently carried out and would save the National Health Service considerable expense. The test would also be less traumatic for the patient than having cystoscopy, which is an uncomfortable, time consuming procedure. As males are becoming more aware of their own health, the test could also be used to screen males over 50 years, as this is the group most at risk from bladder cancer. It is hoped that a urinary dip-stick will allow quick detection of the presence of a bladder tumour.

The high frequency of recurrent TCC in the bladder and the progression to a more malignant phenotype in a

proportion of patients means that lifetime follow-up using cystoscopy and urinary cytology is essential. Cystoscopy is an invasive procedure and urinary cytology while non-invasive is relatively insensitive. At present the Bard BTA and STAT tests are the only commercially available detectors for bladder cancer. Their sensitivity means that at best they will only act in conjunction with cystoscopy. The Bard TRAK test while more sensitive has yet to be marketed and in fact the results from the present study indicate that the 37KDa EGFR fragment is at least comparable. Further work is required to investigate the significance of this fragment in the detection of first presentation and recurrent bladder TCC and to determine whether making it into a quantitive test will offer some insight into prognosis. Appropriate applications are detailed below.

The 37KDa EGFR fragment may be used as a detector for first presentation bladder and recurrent bladder TCC. Detection of the 37KDa EGFR fragment may be carried out by other methods of investigation as well as western blot analysis. These methods may include immunochromatography, ELISA, latex agglutination or radioimmunoassay. There is currently available a one-step immunochromatographic assay which qualitatively detects bladder tumour antigen in urine in five minutes. Detection of the 37KDa EGFR fragment may be detected by a similar method. Patient urine would be added to the small chamber where it mixes with a colloidal gold-conjugated antibody. If the 37KDa fragment is present, a 37KDa fragment conjugate complex would form. The reaction mixture would flow through the membrane which contains zones of immobilised capture antibodies. In the test zone, the 37KDa fragment conjugate complexes would be captured by a

second antigen-specific antibody, forming a visible line. If the 37KDa fragment is not present in the urine, no visible line would form.

EGF-Receptor (Ab-4) is available from Oncogene Science, Inc. as catalogue no. HCS16. There is no suggestion that the antibody could be used to diagnose the presence of the 37KDa EGFR fragment in urine or that the presence of this fragment is indicative of bladder or prostate cancer.

Other antibodies can be developed which are specific to the 37KDa fragment. This may increase sensitivity of the test.

A dip-stick test may be developed. This may require using methods such as latex agglutination, immunochromatogrphy, ELISA and radioimmunoassay.

Bladder cancer prognosis has been correlated with a number of factors, the single most important of which is depth of invasion of the bladder wall (Gospodarowicz, 1995); this is followed by grade of tumour (Heney et al., 1983). Other less important factors which influence patient outcome include tumour size (Gospodarowicz, 1995), age of patient at diagnosis (Fitzpatrick and Reda, 1986) and health status (Thrasher et al, 1994). None of these factors can predict prognosis in 100% of patients and so the 37KDa fragment may have some use prognostically. The EGFR fragment may be detected quantitatively using densitometry following western blot analysis and used to predict whether increased levels indicate a better or worse prognosis. Other quantitative methods may be developed to allow easier performance e.g. ELISA or radioimmunoassay techniques.

EGF and EGFR have been implicated in the pathogenesis of solid tumours such as those of the breast. This simple test developed for urine of patients with suspected TCCB might also be used to identify the diagnostic prognostic role of serum EGFR in other tumour types.

**CLAIMS**

1. A marker for bladder cancer, prostate cancer or urinary infection, the marker consisting a 37KDa fragment of EGFR.

2. A method for the diagnosis of first presentation or recurrence of bladder cancer, the method consisting of the detection of a 37KDa fragment of EGFR in a urine sample.

3. A method as claimed in claim 2 wherein the presence of the 37KDa EGFR fragment is detected using an antibody.

4. A method as claimed in claim 2 or claim 3 wherein the presence of 37KDa EGFR fragment is detected using antibody Ab4 EGFR available from Oncogene Science, Inc.

5. The use of antibody Ab4 EGFR in a test to detect the presence of 37KDa EGFR fragment in urine as a diagnostic test for bladder cancer.

6. A method for the diagnosis of prostate cancer, the method comprising the detection of a 37KDa fragment of EGFR in a urine sample.

7. A method as claimed in claim 6 wherein the presence of the 37KDa EGFR fragment is detected using an antibody.

8. A method as claimed in claim 6 or claim 7 wherein the presence of 37KDa EGFR fragment is detected using antibody Ab4 EGFR available from Oncogene Science, Inc.

9. The use of antibody Ab4 EGFR in a test to detect the presence of 37KDa EGFR fragment in urine as a diagnostic test for prostate cancer.

10. A method for the diagnosis of bladder cancer, and/or prostate cancer and/or urinary infection, the method comprising a test for the presence of a 37KDa fragment of EGFR in a urine sample.

11. A method as claimed in any of claims 2 to 4 and 7 to 10 in the form of a dip-stick test.

12. The use of antibodies to the 37KDa fragment of EGFR in the diagnosis of urinary infection, bladder cancer and prostate cancer.

# DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

ned inventor, " hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled EGFR 37 KDA FRAGMENT AS CANCER MARKER, the specification of which

☐ is attached hereto

☒ was filed on: September 30, 1999
as Application Serial No.: PCT/GB99/03235

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the cl as amended by any amendment referred to above.

dge the duty to disclose to the Patent Office all information known to me to be material to patentability 37 C.F.R. 1.56.

foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for tor's certificate listed below and have also identified below any foreign application for patent or ificate having a filing date before that of the application on which priority is claimed:

Application(s)

| (Number) | (Country) | (Day/Month/Year Filed) | Priority Claimed |
|---|---|---|---|
| 9821170.9 | GB | 09/30/98 | ☒ Yes ☐ No |
| | | | ☐ Yes ☐ No |

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Patent Office all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which occurred between the filing date of the prior application and the national or PC international filing date of this application:

| (Application Serial No.) | (Filing Date) | (Status: patented, pending, abandoned) |
|---|---|---|

the following attorneys to prosecute this application and to transact all business in the Patent and ice connected therewith: Harold C. Hohbach, Reg. No. 17,757; Aldo J. Test, Reg. No. 18,048; clmosh, Reg. No. 20,316; Edward S. Wright, Reg. No. 24,909; David J. Brezner, Reg. ber; B. Chickering, Reg. No. 24,286; Richard F. Trecartin, Reg. No. 31,801; Steven F. Caserza, ; Michael A. Kaufman, Reg. No. 32,988; Edward N. Bachland, Reg. No. 37,085; R. Michael o. 35,050; Robin M. Silva, Reg. No. 38,304; David C. Ashby, Reg. No. 36,432; Maria S. Swistak, Reg. No. 37,244; Todd A. Lorenz, Reg. No. 39,754, provided that if any one of said attorneys ceases being affiliated with the law firm of Flehr Hohbach Test Albritton & Herbert LLP as partner, employee or of counsel, such attorney's appointment as attorney and all powers derived therefrom shall terminate on the date such attorney ceases being so affiliated.

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...9/REI

...at all statements made herein of my own knowledge are true and that all statements made on ... and belief are believed to be true; and further that these statements were made with the knowledge ... false st...tements and the like so made are punishable by fine or imprisonment, or both, under Title 18, ...tes Code §1001 and that such willful false statements may jeopardize the validity of the application or ... issued thereon.

1 - CO

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